Remarks

Claims 1-57 and 82-103 are pending in the application. Claims 1, 82-83, 86-88, and 95 are here amended. Support for these amendments can be found in the specification, e.g. on page 33, lines 27-28, and in the claims as originally filed. The Office Action is properly non-final, as it raises new grounds of rejection. No new matter is added by the amendments to the claims.

Issues under 35 U.S.C. § 112

The Office Action on page 2 ¶ 4 rejects claims 1-22, 82-83, 86-93, and 95-101 under 35 U.S.C. § 112, second paragraph. The claims have been amended to remove the phrase cited by the Examiner.

Claims 1, 82-83, 86, 88, and 95 as here amended are directed to a modified biological molecule following reaction with a compound having the formula $R_1 — X — R_2$ that is soluble in aqueous solution. Claims 2-22, 89-94, and 96-101 depend directly or indirectly from claims 1, 88, or 95, therefore dependent claims incorporate the amendments to claims 1, 82-83, 86, 88, and 95.

Applicants assert that the language of the claims as here amended is clear. Therefore, Applicants respectfully request that this rejection be withdrawn.

Applicants believe that it would be helpful to the Examiner to summarize the subject matter of the claims as here amended, before discussing prior art cited in the Office Action.

Invention of the present claims

Claims as here amended are directed to modified biological molecules, *e.g.*, modified nucleic acids and modified analogs or mimetics thereof, modified polysaccharides and modified analogs or mimetics thereof, modified lipids and modified analogs or mimetics thereof, that are reacted with a compound of formula of $R_1 — X — R_2$, in which R_1 is a cyclic ether group or an amino group, R_2 is an alkoxysilane group and X is a moiety chemically suitable for linking the cyclic ether group or the amino group to the alkoxysilane group. The modified molecule which is the result of the reaction is not attached to any solid phase surface, i.e., is not immobilized. Instead, the modified molecule of the present claims is soluble in the aqueous solution of the

reaction in which it was produced. In this solution form, the modified biological molecules can be printed in an array format reliably and reproducibly onto replicates of surfaces, and onto a variety of different surfaces, and can be conveniently stored and reaccessed for repeated later use.

Because products of this reaction are spotted on surfaces, the chemical reaction that immobilizes these modified biological molecules occurs only at that limited area of the spot. As a result, when reactions such as hybridizations using nucleic acid samples are subsequently performed with these arrays made with these modified molecules, a high contrast is obtained between the successful hybridized molecules and the background. Hybridization is specific to the areas of ligand spots, and remaining areas of the underivatized substrate have reduced non-specific binding, compared to the surfaces used in the prior art which are derivatized and are therefore more non-specifically reactive.

Claims are novel

Plueddemann et al., U.S. patent number 4,231,910

The Office Action on page 2 ¶ 5 rejects claims 1-7, 12-15, 18-19, 84-85, and 88-91 under 35 U.S.C. 102(b) as anticipated by Plueddemann. The Examiner on page 3, ¶ 1 of the Office Action alleges that Plueddemann teaches a modified biological molecule which is a DNA primer composition, bound to a compound having the formula $R_1 — X — R_2$. Applicants traverse.

Plueddemann is not the same as the present claims because this reference does not disclose nucleic acids, nucleic acid primers, or biological molecules of any kind, let alone such molecules modified as described in the present claims, and let alone such modified molecules that are soluble in aqueous solution. Applicants point out that Plueddemann's abstract defines the term "primer compositions" as used in that reference:

> A primer composition consisting essentially of 75-99 percent alkoxymethyltriazine and 1 to 25 percent 3-glycidoxypropyltrimethoxysilane, 2(3,4-epoxycyclohexyl)-ethyltrimethoxysilane, 3-mercaptopropyltrimethoxysilane, 2-mercaptoethyltrimethoxysilane or a partial hydrolyzate of the silanes is employed to improve wet and dry adhesion of thermoplastics to solid substrate. [Emphases added.]

A composition that is 75-99 percent alkoxymethyltriazine and 1-25% of one or more organic silanes is simply not a biological molecule, let alone a nucleic acid primer. Applicants assert that Plueddemann does not disclose biological molecules, let alone a modified biological molecule as in the present claims, and therefore this reference does not anticipate the present claims. Plueddemann's "primer" is for priming surfaces in preparation of applying an adhesive, and relates to a different art than the modified biological molecules of the present claims.

None of claims 1, 84-85, and 88, directed to various embodiments of a modified biological molecule, nor claims 2-7, 12-15, 18-19, and 87-91 which depend directly or indirectly from claims 1 or 88, are anticipated by Plueddemann et al. Applicants respectfully request that this rejection be withdrawn.

Beattie et al. U.S. patent number 6,426,183

The Office Action on page 3 ¶ 5B of the Office Action rejects claims 1-9, 11-15, 18, 20-36, 38-39, 47, 82-91, 94-97, and 99-103 under 35 U.S.C. § 102(e) as anticipated by Beattie et al.

The Office Action on page 4 of the Office Action rejects claims 1 and 95 and their dependent claims 8-9, 11-15, and 94-101 as anticipated by Beattie et al. The Examiner alleges that Beattie et al. at column 18, lines 52-65 describes a compound having formula $R_1 — X — R_2$, wherein R_1 is a cyclic ether group, more specifically, an epoxy group.

Claims 1 and 95 as here amended, and claims 2-9, 11-15, 18, 20-22 and 94-101 which depend directly or indirectly from claim 1 or 95, are directed to a composition which includes a nucleic acid or an analog or a mimetic of a nucleic acid, a polysaccharide or an analog or a mimetic of such, a lipid or an analog or a mimetic of such, or a peptidomimetic or nonbiopolymeric small molecule, or biological molecule, which is modified by reaction with a compound of the formula $R_1 — X — R_2$ described wherein R_1 is a cyclic ether. Beattie et al. simply does not show a modified biological molecule having the formula $R_1 — X — R_2$ and soluble in aqueous solution.

Instead, Beattie in column 18, lines 52-65 refers to a compound having formula $R_1 — X — R_2$, wherein R_1 is an amino group, R_2 is a hydroxy group, and X is a linker connecting R_1 and R_2. Most importantly, this compound in Beattie is not bound to a biological molecule such as a nucleic acid. Rather, the Beattie compound is bound to a commercially available bead commonly used as a support for oligonucleotide synthesis. Further, during synthesis, the initial

product as it is made bound to the support (i.e., a bead or a resin) for the synthesis step, and is only subsequently cleaved off prior to use. In neither of these stages is the structure the same as that of the modified biological molecules of the present claims.

Fig. 1 of Beattie et al. shows construction of 3'-aminopropanol derivatized oligomers (9-mers). Beattie at column 16, lines 25-37 states:

> Introduction of a primary amine function onto the 3'-terminus of an oligonucleotide can be conveniently accomplished by the use of a special CPG support available from Clontech ("3'-Amine-ON^{TM}CPG") or Glen Research ("3'-Amino-Modifier C3 CPG"). During post-synthetic incubation of this support in concentrated ammonia, the Fmoc protecting group is cleaved to generate function at the 3' end of the oligonucleotide, and a 3'-OH group is simultaneously generated by the cleavage of the succinate linkage to the glass. Since the pendant amine and hydroxy functions are on the carbon atoms 2 and 3 in the C3 linker, the resulting derivitization is actually a 3'-propanolamine or 3'-aminopropanol, as shown in Fig. 1. [Emphases added.]

Beattie et al. fails to show a compound of the formula $R_1 — X — R_2$ wherein R_1 is a cyclic ether. Further, Beattie fails to show any modified molecule that is soluble in aqueous solution. As Beattie is not the same as claims 1 and 95, therefore Beattie does not anticipate claims 1 and 95, and does not anticipate dependent claims 8-9, 11-15, and 94-101 which depend directly or indirectly from claims 1 and 95.

Claims 23, 30-36, 38-39, and 47 are rejected as anticipated by Beattie et al.

Claim 23 as here amended is directed to an article of manufacture comprising an arrayed plurality of biological molecules that are modified by reaction with a compound $R_1 — X — R_2$, wherein R_1 is a cyclic ether group or an amino group, R_2 is an alkoxysilane group and X is a moiety chemically suitable for linking the cyclic ether group or the amino group to the alkoxysilane group, and the biological molecules are modified by reaction before attachment to the surface. See claim 23 as here amended and as originally filed, line 3.

The commercially available bead used by Beattie, for standard synthesis of oligonucleotides, is a solid support. Beattie refers to synthesis of oligonucleotides having an additional chemical group at one end, the 3' end. To synthesize such oligonucleotides Beattie attaches the precursor to a special CPG support (CPG stands for Controlled Pore Glass). A subsequent reaction with ammonia produces the oligonucleotide having 3'-propanolamine or 3'-

aminopropanol. Thus the oligonucleotide is not soluble in aqueous solution, but immobilized on a bead.

Further, claim 23 is directed to an article of manufacture having an arrayed plurality of biological molecules, such that each of the biological molecules previously modified is attached to the surface of at least one discrete and known locations. There is no array in Beattie's commercially available supports. Beattie et al. simply does not show the subject matter of claim 23 as here amended.

For any of these reasons, claim 23, and claims 24-28, 30-36, 38-39 and 47 which depend directly or indirectly from claim 23 are not anticipated by Beattie.

Claims 84 and 85 are rejected in the present Office Action. Each of these claims includes the feature that a biological molecule is modified by reaction with a compound having the formula: $R_1 — X — R_2$, wherein R_1 comprises a cyclic ether group (comprising an oxirane in claim 84, and comprising an aromatic hydrocarbon epoxide group in claim 85). Beattie et al. does not show any cyclic ether group. Therefore, Beattie does not anticipate claims 84 or 85.

Claims 86-88 are rejected in the Office Action. Claims 86-88 as here amended are directed to a biological molecule modified by reaction with a compound with a formula of $R_1 — X — R_2$, the modified molecule being soluble in aqueous solution. Beattie et al. simply does not show this molecule, and does not show this molecule which is soluble in aqueous solution. Therefore, Beattie does not anticipate claims 86-88.

The Office Action on page 3 rejects ¶ 5B rejects claim 103, which is directed to a method for making an article of manufacture having a biological molecule that is reacted with a compound of a formula of $R_1 — X — R_2$, wherein R_1 is an amino group, R_2 is an alkoxysilane group and X is a moiety chemically suitable for linking the cyclic ether group or the amino group to the alkoxysilane group, the biological molecules reacted with the compound before attachment to the surface.

Beattie et al. simply does not show an article of manufacture comprising biological molecules that have been modified before attachment to a surface, by reaction with a compound having formula $R_1 — X — R_2$, wherein R_1 is a cyclic ether group or an amino group, R_2 is an alkoxysilane group and X is a moiety chemically suitable for linking the cyclic ether group or the amino group to the alkoxysilane group, nor compositions that are such modified molecules, nor methods of performing such reactions.

Beattie et al. does not show such a method because, as shown above, the reaction in Beattie is a synthesis that occurs by reaction with a precursor that is immobilized on a solid surface. Beattie is not the same as claim 103. Therefore, Beattie et al. does not anticipate claim 103.

Beattie et al. is not the same as the claims as here amended, and therefore does not anticipate the claims as amended. Applicants request that this rejection be withdrawn.

Rauh et al., U.S. patent number 5,401,415

The Office Action on page 4, ¶ 5C of the Office Action rejects claims 1-6, 10, 18, 19, 23 and 37 under 35 U.S.C. § 102(b) as anticipated by Rauh et al. The Examiner alleges that Rauh et al. teaches a modified biological molecule covalently bound to a compound having the formula $R_1 — X — R_2$, wherein R_1 comprises a cyclic ether group or an amino group, R_2 comprises an alkoxysilane group, X comprises a linking moiety, wherein the cyclic ether group is an epoxy group. The Examiner cites column 6, lines 26-67, and column 7, lines 15-52 of Rauh. Applicants respectfully disagree.

Rauh et al. refers to binding a moiety to a surface (*viz.*, by reaction while immobilized to a glass bead) so that the resulting reacted moiety remains immobilized. Rauh then binds cholesterol to this modified bead surface. (*See* Rauh et al., column 6, lines 26-67, and column 7, lines 15-52 of Rauh et al.)

Rauh et al. does not anywhere refer to any biological molecule or any article of manufacture in which, before attachment to the surface, the biological molecule is modified by reaction with a compound having the formula $R_1 — X — R_2$, with R_1 is a cyclic ether group or an amino group, R_2 is an alkoxysilane group and X is a moiety chemically suitable for linking the cyclic ether group or the amino group to the alkoxysilane group.

Rauh et al. shows compound $R_1 — X — R_2$ only as it is attached to a glass bead. The beads after reaction are exposed to a sample containing cholesterol, and can then bind the cholesterol to the bead. (*See* Rauh, column 6, lines 26-67, and column 7, lines 15-52 of Rauh et al.).

Rauh simply does not show any biological molecule modified by reaction with a compound having the formula $R_1 — X — R_2$, wherein R_1 comprises a cyclic ether group or an amino group, R_2 comprises an alkoxysilane group, and X comprises a moiety for linking the

cyclic ether group or the amino group to the alkoxysilane group, and the modified biological molecule is soluble in aqueous solution. All of Rauh's reactions are immobilized to the solid phase bead and are therefore not in solution.

Claim 1 and dependent claims 2-6, 10, and 18-19 are not anticipated by Rauh et al. Therefore, Applicants request that the rejection of these claims in view of Rauh et al. be withdrawn.

Claims 23 and 37 are rejected under 35 U.S.C. § 102 as anticipated by Rauh et al. Claim 23 as here amended is directed to an article of manufacture comprising an arrayed plurality of biological molecules that are modified by reaction with a compound $R_1 — X — R_2$, wherein R_1 is a cyclic ether group or an amino group, R_2 is an alkoxysilane group and X is a moiety chemically suitable for linking the cyclic ether group or the amino group to the alkoxysilane group, the biological molecules being modified by reaction before attachment to the surface

Rauh et al. refers to beads coated with compound (*See* column 6, lines 25-26 of Rauh et al.), and not to an arrayed plurality of biological molecules as in claim 23. An array is defined in the American Heritage Dictionary of the English Language as, "An orderly, often imposing arrangement." In contrast, the American Heritage Dictionary of the English Language defines a coating as, "A layer of a substance spread over a surface for protection or decoration; a covering layer."

Rather than referring to an arrayed plurality, Rauh's bead is randomly covered with a compound able to bind cholesterol, in order to measure total cholesterol in a sample. Rauh et al. does not disclose or teach or suggest an article of manufacture comprising an arrayed plurality of biological molecules.

As the standard for rejection under 35 U.S.C. 102 is identity, and Rauh et al. does not disclose or teach or suggest the subject matter of claim 23, Rauh does not anticipate claim 23, nor does Rauh anticipate claim 37 which depends from claim 23 and incorporates all of the features of claim 23.

Applicants request that the rejection of claims under 35 U.S.C. 102(b) in light of Rauh be withdrawn.

Gray et al. U.S. patent number 5,851,769

The Office Action on page 8, ¶ 9C rejects claims 1-3, 11-15, 18, 20, 22, 95, and 100-101 under 35 U.S.C. § 102(e) as being anticipated by Gray et al.

Gray describes methods for physical mapping and positional cloning of DNA, particularly "stretched" DNA, and uses the hydrodynamic force of a receding meniscus to prepare straight high molecular weight DNA molecules for in situ hybridization. See Gray column 14, lines 9-13. Stretching is uniform for DNA fibers of 17 kb to over 1000 kb (column 16, lines 26-28). Gray treats surfaces (slides) with 3-aminopropyltriethoxysilane (APS): column 19, lines 49-51.

Gray simply does not modify the DNA nor any other biological molecule with APS or any other such reagents, and therefore is not the same as the present claims. Rather, Gray typifies the art prior to the present invention, in that Gray treats an entire surface with APS, and does not treat any biological molecule of interest with APS.

The Examiner states that alkoxysilane would have the same inherent properties since the structure is the same. Claims 1 and 95 as here amended are directed to a modified biological molecule which has been modified by reaction with an $R_1 — X — R_2$ compound, and not to an alkoxysilane per se prior to reaction.

Because Gray et al. is not the same as the subject matter of claims 1 or 95, or claims that depend directly or indirectly from these claims, Gray does not anticipate claims 1-3, 11-15, 18, 20, 22, 95, and 100-101.

Applicants request that rejection of claims as anticipated be withdrawn.

Claims are non-obvious

The Office Action on page 5, ¶ 6 of the Office Action rejects claims 16-17 and 40-57 under 35 U.S.C. § 103(a) over Beattie et al. in light of Lockhart et al., U.S. patent number 6,040,138. Applicants traverse.

Beattie et al. as characterized above refers to methods of attaching derivatized nucleic acids to a surface derivatized with an alkoxysilane. The claims as here amended are directed to compositions, methods and articles in which biological molecules are modified by reaction with alkoxysilane and are soluble in aqueous in solution, i.e., are not immobilized to a solid substrate. In contrast Beattie derivatizes a surface with alkoxysilane. Thus, the methods of Beattie make it

likely that other molecules encountering such a derivatized surface, for example molecules in a test sample, will stick non-specifically to the alkoxysilane immobilized along entire surface. By derivatizing the biological molecule with alkoxysilane prior to forming a cluster, the arrays and methods of the claims herein avoid this problem.

Beattie et al. teaches away from the instant claims (in column 16, lines 48-63, and Figure 2) because Beattie teaches that the 5'-amino and 3'-aminopropanol 9-mers bind to epoxysilanized glass, but not to underivatized glass. Beattie shows hybridization of probe where the 9-mers were spotted on epoxysilanized glass (Figure 2B), and lack of hybridization where the 9-mers were spotted on control untreated (underivatized) glass (Figure 2C).

Beattie et al. does not disclose, teach, or suggest the compositions, methods, and articles of manufacture of the instant claims. Instead, Beattie produces the very technical problems that the compositions and articles of the present claims solve. The compositions and articles of the instant claims are structurally and functionally completely unexpected in view of the teachings of Beattie et al.

Lockhart et al., U.S. patent number 6,040,138

Lockhart et al. does not cure the deficiencies of Beattie et al. Lockhart et al. refers to a high density gene array comprising 1000 or more oligonucleotides spotted at predetermined locations.

Lockhart et al. does not teach, suggest or disclose a biological molecule modified by reaction with a compound having the formula of $R_1 — X — R_2$, wherein R_1 is a cyclic ether group or an amino group, R_2 is an alkoxysilane group and X is a moiety chemically suitable for linking the cyclic ether group or the amino group to the alkoxysilane group, wherein the modified biological molecule is soluble in aqueous solution, as is required by claim 1 as here amended, and from which claims 16-17 depend.

Nor does Lockhart et al. teach, suggest or disclose an article or manufacture comprising an arrayed plurality of biological molecules, in which the biological molecule has been reacted with a compound with a formula of $R_1 — X — R_2$, wherein R_1 is a cyclic ether group or an amino group, R_2 is an alkoxysilane group and X is a moiety chemically suitable for linking the cyclic ether group or the amino group to the alkoxysilane group, before attachment to the

surface, as stipulated by claim 23, from which claims 40-57 depend. Lockhart et al. does not cure the deficiencies of Beattie et al.

An practitioner of ordinary skill in the art of making arrays, reading Beattie et al. in view of Lockhart et al., would not be taught to make the compositions and articles of claims 16-17 and 40-57. The practitioner would not have been motivated to overcome the technical problems presented in the arrays of Beattie et al. by combining this reference with the high density array of Lockhart et al. This combination fails even to suggest these problems, let alone a solution to overcome these problems. Claims 16-17 and 40-57 are not obvious over Beattie et al. in light of Lockhart et al.

Applicants respectfully request that this rejection be withdrawn.

Correspondence Address

Applicants request that the correspondence address for this application be changed, pursuant to a revocation/new power of attorney filed in this case on September 30, 2003, to

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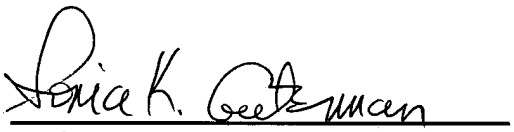
CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested.

Should any questions or issues arise concerning the application, the Examiner is invited and encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,



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